



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61F 2/06, A61M 5/00, 5/24</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/44306</b> <b>(43) International Publication Date:</b> 3 August 2000 (03.08.00)
<b>(21) International Application Number:</b> PCT/US99/22420 <b>(22) International Filing Date:</b> 27 September 1999 (27.09.99) <b>(30) Priority Data:</b> PCT/US99/01790 27 January 1999 (27.01.99) US <b>(71) Applicant (for all designated States except US):</b> THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 12th floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MURAYAMA, Yuichi [US/US]; 17352 Sunset Boulevard, 404-D, Pacific Palisades, CA 90272 (US). VINUELA, Fernando [US/US]; 16100 Sunset Boulevard #101, Pacific Palisades, CA 90272 (US). <b>(74) Agent:</b> DAWES, Daniel, L.; Myers, Dawes & Andras LLP, Suite 650, 650 Town Center Drive, Costa Mesa, CA 92626-1925 (US).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> BIODEGRADABLE POLYMER/PROTEIN BASED COILS FOR INTRALUMENAL IMPLANTS  <b>(57) Abstract</b>  An endovascular cellular manipulation and inflammatory response are elicited from implantation in a vascular compartment or any intraluminal location of a separable coil comprised at least in part of at least one biocompatible and absorbable polymer or protein and growth factors. Typically a catheter associated with the separable coil is used to dispose the coil into a selected body lumen. The biocompatible and absorbable polymer or protein is thrombogenic. The coil further is comprised at least in part of a growth factor or more particularly a vascular endothelial growth factor, a basic fibroblast growth factor or other growth factors. The biocompatible and absorbable polymer is in the illustrated embodiment at least one polymer selected from the group consisting of polyglycolic acid, poly~glycolic acid/poly-L-lactic acid copolymers, polycaprolactone, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-lactide. Polydioxanone, polycarbonates, and polyanhydrides. The biocompatible and absorbable protein is at least one protein selected from the group consisting of collagen, fibrinogen, fibronectin, vitronectin, laminin, and gelatin. In one embodiment the coil is composed of the biocompatible and absorbable polymer or protein with a radio-opaque material is disposed thereon. Alternatively, the coil is composed of a radio-opaque material, and the biocompatible and absorbable polymer or protein is disposed thereon. This apparatus may be positioned within intracranial aneurysms or any aneurysm in the body as well as within other body cavities.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## BIODEGRADABLE POLYMER/PROTEIN BASED COILS FOR INTRALUMENAL IMPLANTS

5

### Background of the Invention

#### *Related Applications*

The present application is related to U.S. Provisional Patent Application  
10 ser. No. 60/072,653 filed Jan. 27, 1998 and to PCT International Appl.No.  
PCT/US99/01790 filed Jan. 27, 1999 upon which its priority is based.

#### *1. Field of the Invention*

The invention relates generally to the field of surgical and endovascular  
15 interventional instruments and specially to Intraluminal implants for occlusion of  
vessels or aneurysms.

#### *2. Description of the Prior Art*

Brain aneurysms are the commonest cause of nontraumatic subarachnoid  
20 hemorrhage (SAH) which is a significant life-threatening disease in adults.  
Annually in North America, the rupture of saccular aneurysms accounts for  
25000 new cases of SAH. Microsurgical clipping of an aneurysm has been  
considered the gold standard for the treatment of this disease. Recently,  
intravascular treatment of aneurysms has become an accepted alternative  
25 technique. With the availability of microcatheters capable of accessing the

intracranial circulation it has become possible to obliterate an aneurysm by filling it with soft platinum detachable coils (Guglielmi Detachable Coils; GDC). Use of the GDC system allows controlled delivery and detachment of platinum coils within an aneurysm.

5           Recent advances in endovascular techniques have proved valuable in the treatment of cerebral saccular aneurysms. GDCs have contributed especially to improvements in the endovascular management of cerebral aneurysms.

However, the size of an aneurysm neck has an important effect on the anatomic results of aneurysm obliteration. It has been reported that in one study complete  
10   obliteration of aneurysms was achieved in 85% of small-necked aneurysms and 15% of wide-necked aneurysms.

Early experience with experimental and clinical use of Guglielmi detachable coils (GDCs) as manufactured by Target Therapeutics, Fremont, California, points to their effectiveness in the occlusion of endovascular small-  
15   necked intracranial saccular aneurysms.

However, the anatomical results of obliteration of either wide-necked (neck size  $\geq 4$  mm) or giant aneurysms using GDCs are generally unsatisfactory. The reasons for these incomplete anatomical results in wide-necked lesions include coil compaction, aneurysmal recanalization and the potential for distal  
20   migration of detached coils, i.e. the downstream loss of the coils from the aneurysm. Early intravascular re-endothelialization at the necks of aneurysms and the acceleration of wound healing in the aneurysmal sac and dome are

potential solutions that may help achieve successful permanent cures of this type of aneurysm.

Some investigators have applied simple protein coatings on GDCs to enhance their thrombogenicity and wound healing properties. However, 5 intravascular embolization techniques generally make use of small-diametered microcatheters for delivery of these coils. Simple protein coating, therefore, results in the problem of increasing the diameter of these coils which in turn causes them to stick within the lumen of a microcatheter during coil delivery.

Occlusion coils are used to occlude a site within a body lumen, such as a 10 blood vessel, brain aneurysm, or vascular malformation. The coils are typically placed at a desired site within the lumen by means of a microcatheter. The coils are normally made of a radioopaque, biocompatible metals such as platinum, gold, or tungsten. In treating brain aneurysms the coils occlude the aneurysm by posing a physical barrier to blood flow and by promoting thrombus formation. 15 The formation of the neo-endothelium and mature intra-aneurysmal thrombus is necessary prior to subsequent organization and scar formation that, in turn, yields a permanently occluded aneurysm.

In the presence of continued exposure of intra-aneurysmal coils to circulating blood, metallic coils can be insufficiently thrombogenic to promote the 20 establishment of firm and mature thrombus within the aneurysm. They have difficulty in promoting endothelialization across the wide neck of an aneurysm. Therefore, it is advantageous to tightly pack the aneurysm with coils for complete

cure of the aneurysms. This may cause a mass effect on adjacent th brain parenchyma or cranial nerves.

To accelerate wound healing in the aneurysm (i.e., promotion of scar formation) and to decrease the mass effect of the aneurysm, "biologically active" bioabsorbable embolic material may be useful. Bioabsorbable polymers, such as polyglycolic acid and polyglycolic/poly-L-lactic acid copolymers, or bioabsorbable proteins, such as collagen and gelatins, have been used to make Intraluminal implants. These bioabsorbable polymers or proteins are also used to provide a the drug delivery vehicle (such as for continuous local delivery of growth factors).

10 It is necessary to modify biological cellular response in preparation for acceleration of wound healing. Coil thrombogenicity was enhanced previously by increasing the surface area of the coils with fabric strands, such as Dacron, and by placing such coils into a thrombin solution. More recently, some investigators have modified the surfaces of platinum coils by coating them with collagen or  
15 polyurethane. This has resulted in some advantages, such as an increase in thrombogenicity of these coils. However, protein coatings on platinum surfaces are usually weak and may be removed easily during the delivery of the coils. Additionally, weakly coated proteins may be washed off by high-velocity arterial flow and may be a potential source of distal thromboemboli. There is also the  
20 potential problem of increases in the diameters of these coils; polyurethane coatings in particular also have the disadvantage of producing unfavorable changes in GDC performance, affecting their softness, thinness, smoothness, and memory shape.

In summary, GDCs and surrounding thrombus within an aneurysm are continuously exposed to and interact with circulating blood at the neck of the aneurysm. Coil compaction resulting from the force of pulsatile arterial blood flow is one of the reasons for incomplete obliteration of aneurysms. When this occurs, there is a potential risk of aneurysm recanalization and (re)rupture. Re-endothelialization and the promotion of wound healing in the aneurysmal sac and across its neck are necessary for complete aneurysm cure. Despite the many advantages of GDCs in the treatment of aneurysms, several recent clinical and experimental reports have highlighted their potential limitations in achieving an anatomic cure for wide-necked lesions. For example, two human autopsy cases treated with GDCs were reported for which the long-term (up to 6 months) histological findings revealed unorganized thrombus in the aneurysms, with no evidence of endothelialization across the aneurysmal neck in either case. Others have reported the histological findings for a patient with an anterior communicating artery aneurysm that had been previously treated with GDCs, in whom the compaction of coils resulted in an aneurysm remnant that was subsequently (6 months later) treated surgically. Histological examination of this resected aneurysm also revealed the presence of unorganized intra-aneurysmal thrombus that was exposed directly to the blood circulation without neointimal formation. It has been reported that in a long-term GDC study with experimental canine aneurysms, three of nine initially completely embolized aneurysms yielding to subsequent recanalization. Experimental GDC studies in monkey aneurysms were reported in which one of four of cases at 14 days of follow-up

showed an aneurysmal "shoulder," indicative of aneurysm recanalization. More recently, in a study of experimental bifurcation aneurysms in rabbits, demonstrated the absence of organized thrombus and no neck endothelialization in treated aneurysms, even after follow-up periods of 3 to 6 months.

- 5           What is needed is a method to promote an inflammatory response and healing of the aneurysm with reduction of its mass effect.

### **Brief Summary of the Invention**

The invention is an intravascular device that modifies either accelerating  
10 or decreasing biological cellular response comprising a separable tip or coil comprised at least in part of at least one biocompatible and absorbable polymer or protein, and a placement device associated with the separable coil adapted to dispose the coil into a selected body lumen. The biocompatible and absorbable polymer or protein promotes an intra-aneurysmal inflammatory response and  
15 healing of the aneurysms. This device may carry growth factors, such as a vascular endothelial growth factor, a basic fibroblast growth factor or a mixture of several growth factors or cytokines. The separable tip, which also need not be a coil, need not be comprised of a polymer or protein, but may be comprised of any material now known or later devised which is biocompatible, absorbable and  
20 which promotes an intra-aneurysmal inflammatory response and promotes healing of the aneurysm.

The biocompatible and absorbable polymer is in the illustrated embodiment at least one polymer selected from the group consisting of



polyglycolic acid, poly-glycolic acid/poly-L-lactic acid copolymers, polycaprolactone, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-lactide, polydioxanone, polycarbonates, and polyanhydrides.

The biocompatible and absorbable protein is at least one protein selected from the group consisting of collagen, fibrinogen, fibronectin, vitronectin, laminin, and gelatin.

In one embodiment the coil is composed of the biocompatible and absorbable polymer or protein with a radio-opaque material is disposed thereon. Alternatively, the coil is composed of a radio-opaque material, and the biocompatible and absorbable polymer or protein is disposed thereon.

The invention is also characterized as a method for forming a thrombus comprising the steps of providing a separable coil comprised at least in part of at least one biocompatible and absorbable polymer or protein and disposing the separable coil into a body lumen including the various combinations and examples described above.

The method further of comprises the step of providing the coil with a growth factor, and in particular a vascular endothelial growth factor (VEGF), a basic fibroblast growth factor (bFGF), or other growth factors.

The invention having been briefly summarized by the foregoing, the invention and its various embodiments may be better visualized by turning to the following drawings wherein like elements are referenced by like numerals.

#### **Detailed Description of the Preferred Embodiments**

In the present invention a biodegradable polymer (or protein) coils are used to control thrombosis or accelerate wound healing of the brain aneurysms for which platinum coils sometimes have often proven unsatisfactory.

Another aspect of the invention is a method of drug delivery system using  
5 biodegradable polymer (or proteins) in the combination with growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) or other growth factors which promote long lasting effect of the wound healing

These biodegradable coils are useful for treating giant brain aneurysms to  
10 prevent the mass effect on the brain parenchyma or cranial nerves by shrinkage of scaring aneurysm.

#### *Modes For Carrying Out The Invention*

The implants of the invention may be placed within body lumens, e.g.,  
15 blood vessels, Fallopian tubes, etc., of any mammalian species, including humans. The implant coils are made of biocompatible and absorbable polymers or proteins. Examples of bioabsorbable polymers that have been used in the illustrated embodiment to make Intraluminal implants include but are not limited to polyglycolic acid, poly-D-glycolic/poly-L-lactic acid copolymers, polycaprolactone,  
20 polyhydroxybutyrate /hydroxyvalerate copolymers, poly-L-lactide, polydioxanone, polycarbonates, and polyanhydrides. Examples of bioabsorbable proteins that have been used in the illustrated embodiment to make Intraluminal implants

include but are not limited to collagen, fibrinogen, fibronectin, vitronectin, laminin and gelatin.

To achieve radioopacity, the bioabsorbable polymer coils may be coated or mixed with radioopaque materials such as tantalum or platinum. The

5 bioabsorbable polymer or protein itself may be mounted or coated onto coils or wires of metals such as platinum or nitinol.

Preferred growth factors for use in the invention are the naturally occurring mammalian angiogenic growth such as VEGF, or b-FGF. Mixtures of such growth factors may also be used if desired.

10 The biodegradable polymer coils of the invention can be placed within the body lumen, vascular system or vessels using procedures well known in the art. Generally, the desired site within the vessel is accessed with a catheter. For small diameter torturous vessels the catheter may be guided to the site by the use of guide wires. Once the site has been reached, the catheter lumen is

15 cleared by removing guide wire. In the case of polymer occlusion coils, the coils are loaded by means of a pusher wire. The coils may be attached to the distal end of the pusher via a cleavable joint (e.g., a joint that is severable by heat, electrolysis, electrodynamic activation or other means) or a mechanical joint that permits the coil to be detached from the distal end of the pusher wire by

20 mechanical manipulation. Alternatively, the coils may be free and detached from the pusher wire, simply pushed through the catheter and expelled from the distal end of the catheter.

Many alterations and modifications may be made by those having ordinary skill in the art without departing from the spirit and scope of the invention.

Therefore, it must be understood that the illustrated embodiment has been set forth only for the purposes of example and that it should not be taken as limiting  
5 the invention as defined by the following claims.

The words used in this specification to describe the invention and its various embodiments are to be understood not only in the sense of their commonly defined meanings, but to include by special definition in this specification structure, material or acts beyond the scope of the commonly  
10 defined meanings. Thus if an element can be understood in the context of this specification as including more than one meaning, then its use in a claim must be understood as being generic to all possible meanings supported by the specification and by the word itself.

The definitions of the words or elements of the following claims are,  
15 therefore, defined in this specification to include not only the combination of elements which are literally set forth, but all equivalent structure, material or acts for performing substantially the same function in substantially the same way to obtain substantially the same result. In this sense it is therefore contemplated that an equivalent substitution of two or more elements may be made for any one  
20 of the elements in the claims below or that a single element may be substituted for two or more elements in a claim.

Insubstantial changes from the claimed subject matter as viewed by a person with ordinary skill in the art, now known or later devised, are expressly contemplated as being equivalently within the scope of the claims. Therefore,  
25 obvious substitutions now or later known to one with ordinary skill in the art are defined to be within the scope of the defined elements.

The claims are thus to be understood to include what is specifically illustrated and described above, what is conceptionally equivalent, what can be obviously substituted and also what essentially incorporates the essential idea of the invention.

We claim:

1                   1.     An endovascular apparatus of biodegradable and  
2     biocompatible polymers for developing a controlled inflammatory response with  
3     cellular manipulation comprising:  
4                 a separable coil comprised at least in part of at least one biocompatible  
5     and absorbable polymer or protein; and  
6                 an endovascular placement device associated with said separable coil  
7     adapted to dispose said coil into a selected body lumen.

1                   2.     The apparatus of claim 1 wherein said coil further is  
2     comprised at least in part of a growth factor.

1                   3.     The apparatus of claim 2 wherein said coil further is  
2     comprised at least in part of a one selected from the group of VEGF, b-FGF, or  
3     mixtures thereof.

1                   4.     The apparatus of claim 2 wherein said coil further is  
2     comprised at least in part of a basic fibroblast growth factor.

1                    5.     The apparatus of claim 3 wherein said coil further is  
2     comprised at least in part of a mixture of said vascular endothelial growth factor  
3     and a basic fibroblast growth factor.

1                    6.     The apparatus of claim 1 wherein said biocompatible and  
2     absorbable polymer is at least one polymer selected from the group consisting of  
3     polyglycolic acid, poly~glycolic acid/poly-L-lactic acid copolymers,  
4     polycaprolactone, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-  
5     lactide, polydioxanone, polycarbonates, and polyanhydrides.

1                    7.     The apparatus of claim 1 wherein said biocompatible and  
2     absorbable protein is at least one protein selected from the group consisting of  
3     collagen, fibrinogen, fibronectin, vitronectin, laminin, and gelatin.

1                    8.     The apparatus of claim 1 wherein said coil is composed of  
2     said biocompatible and absorbable polymer or protein, and wherein a radio-  
3     opaque material is disposed thereon.

1                    9.     The apparatus of claim 1 wherein said coil composed of a  
2     radio-opaque material, and wherein said biocompatible and absorbable polymer  
3     or protein is disposed thereon.

1                   10.    Th apparatus of claim 1 wherein said biocompatible and  
2   absorbable polymer or protein promotes cellular manipulation, controlled  
3   inflammatory response and vascular healing.

1                   11.    A method for endovascular inflammatory response  
2   comprising:  
3                   providing a separable coil comprised at least in part of at least one  
4   biocompatible and absorbable polymer or protein; and  
5                   disposing said separable coil into a body lumen.

1                   12.    The method of claim 11 further providing said coil with a  
2   growth factor.

1                   13.    The method of claim 12 wherein providing said coil with a  
2   growth factor comprises providing said coil with a vascular endothelial growth  
3   factor.

1                   14.    The method of claim 12 wherein providing said coil with a  
2   growth factor comprises providing said coil with a basic fibroblast growth factor.



1                   15.    The method of claim 13 wherein providing said coil with a  
2   growth factor comprises providing said coil with a mixture of said vascular  
3   endothelial growth factor and a basic fibroblast growth factor.

1                   16.    The method of claim 11 wherein providing said separable  
2   coil comprised with said biocompatible and absorbable polymer comprises  
3   providing said coil with at least one polymer selected from the group consisting of  
4   polyglycolic acid, polyglycolic acid/poly-L-lactic acid copolymers,  
5   polycaprolactone, polyhydroxybutyrate/hydroxyvalerate copolymers, poly-L-  
6   lactide, polydioxanone, polycarbonates, and polyanhydrides.

1                   17.    The method of claim 11 wherein providing said separable  
2   coil comprised with said biocompatible and absorbable protein comprising  
3   providing at least one protein selected from the group consisting of collagen,  
4   fibrinogen, fibronectin, vitronectin, laminin, and gelatin.

1                   18.    The method of claim 11 wherein providing said coil provides  
2   a coil composed of said biocompatible and absorbable polymer or protein with a  
3   radio-opaque material is disposed thereon.

- 1                    19.    The method of claim 11 wherein providing said coil provides  
2    a coil composed of a radio-opaque material with said biocompatible and  
3    absorbable polymer or protein is disposed thereon.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/22420

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61F 2/06; A61M 5/00, 24

US CL : 606/191, 200; 623/1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 623/1; 606/191, 200

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,891,192 A (MURAYAMA et al.) 06 April 1999, col. 1, lines 11-44.	1-19
X,P	US 5,935,145 A (VILLAR et al.) 10 August 1999, col. 2, lines 9-34.	1-19
X, E	US 6,007,573 A (WALLACE et al.) 28 December 1999, col. 3, lines 24-65.	1-19
X,E	US 6,015,424 A (ROSENBLUTH et al.) 18 January 2000, col. 3, lines 37-57/	1-19

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 JANUARY 2000

Date of mailing of the international search report

28 FEB 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3590

Authorized officer

HIEU PHAN

Telephone No. (703) 308-8969